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Immunologic Thrombocytopenic Purpura as Presenting Symptom of Hepatitis C Infection

Frédéric Bauduer,[1]* Fabrice Marty,[2] Marc Larrouy,[3] and Louis Ducout[4]

[1]Service d'Hématologie, Centre Hospitalier de la Côte Basque, Bayonne, France
[2]Service de Médecine 2, Centre Hospitalier de la Côte Basque, Bayonne, France
[3]Laboratoire de Microbiologie-Sérologie, Centre Hospitalier de la Côte Basque, Bayonne, France
[4]Laboratoire d'Hématologie, Centre Hospitalier de la Côte Basque, Bayonne, France

We report on 3 female patients with immunologic thrombocytopenic purpura (ITP) for whom diagnostic procedures evidenced a chronic Hepatitis C virus (HCV) infection. In 2 cases, a transfusion performed more than 10 years ago represented the probable way of contamination. One patient received a course of steroids, which normalized the platelet counts. Another one has been treated with repeated IV immunoglobulins, which induced partial responses of variable duration. HCV is responsible for many autoimmune manifestations and a search for this virus seems warranted for exploring patients with ITP. Am. J. Hematol. 57:338–340, 1998. © 1998 Wiley-Liss, Inc.

Key words: immune thrombocytopenia; hepatitis C; transfusion

INTRODUCTION

Immunologic thrombocytopenic purpura (ITP) can result from many causes including viruses. Hepatitis C virus (HCV) is increasingly implicated in dysimmune disorders [1]. Recently, ITP has been described as a possible complication of HCV infection [2–6]. We report herein 3 cases in which ITP revealed this liver disease.

CASE REPORTS (TABLE I)

All the patients fulfilled the usual criteria for ITP including: less than 100×10^9/l platelets at 2 different times (EDTA-related thrombocytopenia being eliminated), a normal or increased number of megacaryocytes in an otherwise normal bone marrow, and no other causes of peripheral thrombocytopenia such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, primary antiphospholipid syndrome, connective tissue disease, lymphoproliferative disorder, drug toxicity, or viral infection in addition to HCV (HIV, Hepatitis B virus (HBV), and CMV). ALT (normal range: 7–33 IU/l) and AST (10–35 IU/l), gamma-glutamyl transpeptidase (GGT) (7–32 IU/l), alkaline phosphatase (AP) (64–300 IU/l), total bilirubin (<5 mg/l), serum electrophoresis, prothrombin time, and the hemogram were performed as routine investigations. Positivity for HCV was evidenced on 2 ELISA kits (Pasteur Products, Paris, France, and Murex, Châtillon, France). RIBA technique was performed for confirmation. Serum HCV RNA was detected by PCR in all the patients. Viral genotype was determined in patient 3 (3A). None of the 3 individuals presented with evident clinical signs of advanced liver failure.

Patient 1 was a 71-year-old woman who presented in April 1996 with a low platelet count (71×10^9/l) discovered on a systematic hemogram because of general weakness. Her past medical history did not include any risk factor for HCV infection. She had 4.4×10^9/l white blood cells (WBC) and 13.1 g/dl hemoglobin (Hb). Sclerae were slightly jaundiced. No purpuric lesions or bleeding manifestations were evident. Physical examination and ultrasonographies did not reveal liver or spleen enlargement or ascites. At the time of HCV infection diagnosis, AST were: 111 IU/l, ALT: 84 IU/l, AP: 429 IU/l, GGT: 101 IU/l, and total bilirubin: 12.3 mg/l. Up to now, this

*Correspondence to: Frédéric Bauduer, MD, Service d'Hématologie, Centre Hospitalier de la Côte Basque, 64100 Bayonne, France.

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TABLE I. Clinical and Laboratory Characteristics of Three Patients

Case	Age	Initial platelet count	Anti-platelet antibodies	AST/ALT	Serum HCV RNA	Probable HCV duration/contamination	Therapy
1	71	71×10^9/l	+	111/84	+	?	None
2	70	31×10^9/l	+	130/118	+	10 years/transfusion	IV Ig
3	67	44×10^9/l	+	40/33	+	27 years/transfusion	Steroids

woman remains with stable platelet count without any therapy.

Patient 2 was a 70-year-old woman with a past medical history of bladder surgery in 1984 including a postoperative red blood cell (RBC) transfusion. In December 1994, before eye surgery, she had 31×10^9/l platelets, 14.4 g/dl Hb, and 7.1×10^9/l WBC (42% neutrophils, 2% eosinophils, 1% basophils, and 55% lymphocytes). Prothrombin time and APTT were normal. Liver tests showed: AST: 130 IU/l, ALT: 118 IU/l, GGT: 112 IU/l, AP: 129 IU/l, and bilirubin: 10 mg/l. She exhibited some episodes of epistaxis and several purpuric lesions, hepatomegaly (vertical span: 16 cm), and a slight spleen enlargement. In January 1995, a liver biopsy showed evidence of advanced cirrhosis. Up to now, the patient has been receiving IV immunoglobulins (Ig) (December 1994, January-March-May 1995, January 1997, May 1997) in order to maintain platelet count above the 20×10^9/l threshold. After each course, the response, albeit partial, was satisfactory (highest reached level: 97×10^9/l).

Patient 3 was 67 in July 1995 when she was referred to our institution for thrombocytopenia at 44×10^9/l. She had undergone a hysterectomy associated with an RBC transfusion when she was 40. Clinically, the patient demonstrated some discrete purpuric lesions but no spleen or liver enlargement. The rest of the hemogram was unremarkable. Liver biology tests showed: AST: 40 IU/l, ALT: 33 IU/l, AP: 154 IU/l, GGT: 44 IU/l, and bilirubin: 8.2 mg/l. Spleen and liver ultrasonography was normal. She received prednisolone (1 mg/kg/day) from August to November 1995. This therapy induced a normalization of platelet count (233×10^9/l in October). In June 1996, she presented with 91×10^9/l platelets. This patient is lost to follow-up since July 1996.

DISCUSSION

Recent publications suggest that HCV may skew the immune response toward the production of autoantibodies [1]. In 1992, a study reported a prevalence of 19% of anti-HCV positive in 112 ITP patients [2]. In 1995, a French group described a 10% prevalence in 139 tested ITP individuals compared to about 1% in the general population of this country [5]. Among 33 cases of ITP, Pivetti et al. found anti-HCV antibodies in 12 (3 were also anti-HBc positive) [1]. In addition, there are some case reports associating HCV with ITP [2–6]. Linares et al. described 4 patients among 44 ITP cases (9%) who were HCV positive and who initially responded to prednisone [6]. Among 36 cases of virus-induced thrombocytopenia, Dine and Brahimi isolated 14 HCV positive patients [3]. In a Japanese study, a thrombocytopenia ($<150 \times 10^9$/l) was diagnosed in 151 of 368 individuals (41%) with chronic hepatitis C compared with 18.9% in chronic hepatitis B [7]. HCV-associated thrombocytopenia is characterized by a high frequency of elevated titers of platelet-associated IgG (about 90%). There seems to exist a negative correlation between these titers and platelet counts [7]. Interestingly, HCV-RNA has been detected using RT-PCR in the platelets from 11 of 14 patients [7]. Alpha-interferon appears deleterious in HCV-associated ITP [8] while improvement in platelet count has been reported in one paper [4]. In addition, this drug can per se induce ITP appearance [9]. Usually, HCV-associated ITP responds to steroids but prolonged use of these agents is not indicated because of possible enhanced viral replication [10]. IV Ig could be useful for life-threatening situations, albeit other treatments are needed for severe chronic ITP. These data suggest the implication of the virus via an immunologic pathway instead of a hypersplenism-related mechanism. In this report, ITP has appeared at an advanced phase of HCV infection associated with active replication. In conclusion, HCV could represent a potential cause of ITP, and systematic serologic studies for this virus appear warranted for patients with peripheral thrombocytopenia.

REFERENCES

1. Pivetti S, Novarino A, Merico F, Bertero MT, Brunetto MR, Bonino F, Caligaris-Cappio: High prevalence of autoimmune phenomena in hepatitis C virus antibody positive patients with lymproliferative and connective tissue disorders. Br J Haematol 95:204–211, 1996.
2. Silva M, Li X, Cheinquer H, Kolodny L, Radick J, La Rue S, Hill M, de Medena M, Reddy R, Jeffers L, Roach K, Schiff ER, Ahn Y: HCV-associated idiopathic thrombocytopenic purpura (ITP). Gastroenterology 102:A889, 1992.
3. Dine G, Brahimi S: Thrombopénie de l'adulte associé à une sérologie VHC positive. Presse Med 22:269, 1993.
4. Durand JM, Cretel E, Retornaz F, Lefevre P, Kaplanski G, Soubeyrand J: Alpha interferon therapy in thrombocytopenia associated with hepatitis C virus infection. J Hepatol 21:277–279, 1994.

5. Pawlovsky JM, Bouvier M, Fromont P, Deforges L, Duval J, Dhumeaux D, Bierling P: Hepatitis C virus infection and autoimmune thrombocytopenic purpura. J Hepatol 23:635–639, 1995.
6. Linares M, Pastor E, Hernandez F, Montagud M, Blanquer A: Autoimmune thrombocytopenia and hepatitis C virus infection. Am J Hematol 53:284, 1996.
7. Nagamine T, Ohtuka T, Takehara K, Arai T, Takagi H, Mori M: Thrombocytopenia associated with hepatitis C viral infection. J Hepatol 24:135–140, 1996.
8. Bacq Y, Sapey T, Gruel Y, Fimbel B, Degenne D, Barin F, Metman EH: Exacerbation d'un purpura thrombocytopénique auto-immun au cours du traitement par l'interféron alpha chez une femme atteinte d'une hépatite chronique virale C. Gastroenterol Clin Biol 20:303–306, 1996.
9. Murakami CS, Zeller K, Bodenheimer HC, Lee WM: Idiopathic thrombocytopenic purpura during interferon alpha 2b treatment for chronic hepatitis. Am J Gastroenterol 89:2244–2245, 1994.
10. Magrin S, Craxi A, Fabiano C, Simonetti RG, Fiorentino G, Marino L: Hepatitis C viremia in chronic liver disease: Relationship to interferon-alpha or corticosteroid treatment. Hepatology 19:273–279, 1994.